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(54) Title: COMBINATION THERAPY FOR TREATMENT OF DEPRESSION

(57) Abstract

The present invention provides a method for treating a patient suffering from depression, comprising administering to said patient an effective amount of a first component which is a 5-HT_3 receptor antagonist, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor wherein improvement in sexual dysfunction and/or reduction in gastrointestinal side effects is recognized.

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COMBINATION THERAPY FOR TREATMENT OF DEPRESSION

Depression in its many variations has recently become much more visible to the general public than it has previously been. It is now recognized as an extremely damaging disorder, and one that afflicts a surprisingly large fraction of the population. Suicide is the most extreme symptom of depression, but millions of people, not quite so drastically afflicted, live in misery and partial or complete uselessness, and afflict their families as well by their affliction. The introduction of fluoxetine, a serotonin reuptake inhibitor (SRI), was a breakthrough in the treatment of depression, and depressives are now much more likely to be diagnosed and treated than they were only a decade ago.

Depression is often associated with other diseases and conditions, or caused by such other conditions. For example, it is associated with Parkinson's disease; with HIV; with Alzheimer's disease; and with abuse of anabolic steroids. Depression may also be associated with abuse of any substance, or may be associated with behavioral problems resulting from or occurring in combination with head injuries, mental retardation or stroke.

A side effect sometimes associated with serotonin reuptake inhibitors concerns the gastrointestinal system wherein symptoms are often manifested as nausea and occasional vomiting. An additional troubling side effect associated with serotonin reuptake inhibitors is sexual dysfunction. It has been estimated that such sexual dysfunction is as high as 34%. [See F.M. Jacobsen, *J. Clin. Psychiatry*, 53, 119, (1992)]. These side effects often result in depressed patients not maintaining the SRI therapy for a period that is long enough in duration to

recognize any significant improvement in the patient's condition.

A benefit of the present adjunctive therapy is a reduction of the above-noted gastrointestinal side effects and/or improvement of the sexual dysfunction known to be associated with the administration of serotonin reuptake inhibitors. It is believed that such a reduction in gastrointestinal side effects and/or improvement of sexual dysfunction will result in increased patient compliance with the SRI therapy, and ultimately, an improvement in lifestyle.

The present invention provides a method for treating a patient suffering from depression, comprising administering to said patient an effective amount of a first component which is a 5-HT_3 receptor antagonist, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor.

The invention further provides a method for treating a patient suffering from anxiety disorders, premenstrual syndrome (PMS) and anorexia nervosa, comprising administering to said patient an effective amount of a first component which is a 5-HT_3 receptor antagonist, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor.

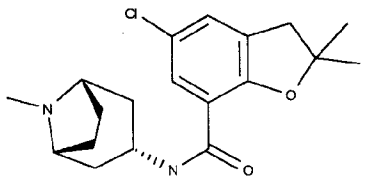
The invention also provides a pharmaceutical composition which comprises a first component which is a 5-HT_3 receptor antagonist, and a second component which is a serotonin reuptake inhibitor.

The above adjunctive therapies of the present invention result in a reduction of gastrointestinal side effects and/or improvement of sexual dysfunction. Thus, the present invention provides the advantage of treatment of depression with a serotonin reuptake inhibitor with a reduction in gastrointestinal side effects or improvement in sexual dysfunction observed with such treatment, conferring a marked and unexpected benefit on the patient.

The Compounds

The first component is a compound which functions as a 5-HT_3 receptor antagonist. 5-HT_3 receptor antagonists include but are not limited to the following compounds:

Zatosetron, endo-5-chloro-2,3-dihydro-2,2-dimethyl-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-7-benzofurancarboxamide, which has the following structure:



U.S. Patent No. 5,563,148, issued October 8, 1996 which is incorporated herein by reference, discloses a preparation of Zatosetron; Olanzapine, a preparation of which is disclosed in U.S. Patent No. 5,229,382, issued July 20, 1993 which is incorporated herein by reference. Also included as 5-HT_3 receptor antagonists are Ondansetron; Granisetron; Bemesetron; Tropisetron; FK1052; YM-060; and MDL 72222. In addition, see EP 0 781 561, published July 2, 1997 and WO 92/00103, published January 9, 1992, which are incorporated herein by reference, for further examples of 5-HT_3 receptor antagonists which are included within the scope of the present invention.

The second component is a compound which functions as a serotonin reuptake inhibitor. The measurement of a compound's activity in that utility is now a standard pharmacological assay. Wong, et al., Neuropsychopharmacology, 8, 337-344 (1993). Many compounds, including those discussed at length above, have such activity, and no doubt many more will be identified in the future. In the practice of the present invention, it is intended to include reuptake inhibitors which show 50% effective concentrations of about 1000 nM or less, in the

protocol described by Wong *supra*. Serotonin reuptake inhibitors include, but are not limited to:

Fluoxetine, N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, is marketed in the hydrochloride salt form, and as the racemic mixture of its two enantiomers. U.S. Patent 4,314,081 is an early reference on the compound. Robertson et al., J. Med. Chem. 31, 1412 (1988), taught the separation of the R and S enantiomers of fluoxetine and showed that their activity as serotonin uptake inhibitors is similar to each other. In this document, the word "fluoxetine" will be used to mean any acid addition salt or the free base, and to include either the racemic mixture or either of the R and S enantiomers;

Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, is usually administered as the hydrochloride salt and as the (+) enantiomer. It was first taught by U.S. Patent 4,956,388, which shows its high potency. The word "duloxetine" will be used here to refer to any acid addition salt or the free base of the molecule;

Venlafaxine is known in the literature, and its method of synthesis and its activity as an inhibitor of serotonin and norepinephrine uptake are taught by U.S. Patent 4,761,501. Venlafaxine is identified as compound A in that patent;

Milnacipran (N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxamide) is taught by U.S. Patent 4,478,836, which prepared milnacipran as its Example 4. The patent describes its compounds as antidepressants. Moret et al., Neuropharmacology 24, 1211-19 (1985), describe its pharmacological activities as an inhibitor of serotonin and norepinephrine reuptake;

Citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, is disclosed in U.S. Patent 4,136,193 as a serotonin reuptake inhibitor. Its pharmacology was disclosed by Christensen et al., Eur. J. Pharmacol. 41, 153 (1977), and reports of its clinical effectiveness in depression may be found in Dufour

et al., Int. Clin. Psychopharmacol. 2, 225 (1987), and Timmerman et al., ibid., 239;

Fluvoxamine, 5-methoxy-1-[4-(trifluoromethyl)-phenyl]-1-pentanone O-(2-aminoethyl)oxime, is taught by U.S. Patent 4,085,225. Scientific articles about the drug have been published by Claassen et al., Brit. J. Pharmacol. 60, 505 (1977); and De Wilde et al., J. Affective Disord. 4, 249 (1982); and Benfield et al., Drugs 32, 313 (1986);

Paroxetine, trans-(-)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine, may be found in U.S. Patents 3,912,743 and 4,007,196. Reports of the drug's activity are in Lassen, Eur. J. Pharmacol. 47, 351 (1978); Hassan et al., Brit. J. Clin. Pharmacol. 19, 705 (1985); Laursen et al., Acta Psychiat. Scand. 71, 249 (1985); and Battegay et al., Neuropsychobiology 13, 31 (1985); and

Sertraline, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine hydrochloride, is a serotonin reuptake inhibitor which is marketed as an antidepressant. It is disclosed by U.S. Patent 4,536,518.

All of the U.S. patents which have been mentioned above in connection with compounds used in the present invention are incorporated herein by reference. It is understood that all of the 5-HT_3 receptor antagonists and serotonin reuptake inhibitors mentioned hereinabove for use in the present invention are readily prepared by one of ordinary skill in the art using known techniques and procedures.

It will be understood that while the use of a single 5-HT_3 receptor antagonist as a first component is preferred, combinations of two or more 5-HT_3 receptor antagonists may be used as a first component if necessary or desired. Similarly, while the use of a single serotonin reuptake inhibitor as a second component is preferred, combinations of two or more serotonin reuptake inhibitors may be used as a second component if necessary or desired.

While all combinations of first and second components are useful and valuable, certain combinations are particularly valued and are preferred, as follows:

Zatosetron/fluoxetine
Zatosetron/venlafaxine
Zatosetron/citralopram
Zatosetron/fluvoxamine
Zatosetron/paroxetine
Zatosetron/sertraline
Zatosetron/milnacipran
Zatosetron/duloxetine
Ondansetron/fluoxetine
Granisetron/fluoxetine

In general, combinations and methods of treatment using Zatosetron as the first component are preferred. Furthermore, combinations and methods of treatment using fluoxetine or duloxetine as the second component are preferred. Especially preferred are combinations and methods of treatment using Zatosetron as the first component and fluoxetine as the second component.

It will be understood by the skilled reader that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

Many of the compounds used in this invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of the compounds of this invention are typically oils at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition

salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid, oxalic acid or fumaric acid.

Preferred pathological conditions to be treated by the present method of adjunctive therapy include depression, bulimia, obsessive-compulsive disease, premenstrual dysphoric disorder, anxiety and obesity. Another preferred condition more specific to combinations including preferably duloxetine but also venlafaxine and milnacipran is urinary incontinence. Depression in all its variations is an especially preferred target of treatment with the present adjunctive therapy and compositions.

Anxiety and its frequent concomitant, panic disorder, may be particularly mentioned in connection with the present compounds. The subject is carefully explained

by the Diagnostic and Statistical Manual of Mental Disorders, published by the American Psychiatric Association, which classifies anxiety under its category 300.02.

Obsessive-compulsive disease appears in a great variety of degrees and symptoms, generally linked by the patient's uncontrollable urge to perform needless, ritualistic acts. Acts of acquiring, ordering, cleansing and the like, beyond any rational need or rationale, are the outward characteristic of the disease. A badly afflicted patient may be unable to do anything but carry out the rituals required by the disease. Fluoxetine is approved in the United States and other countries for the treatment of obsessive-compulsive disease and has been found to be effective.

Obesity is a frequent condition in the American population. It has been found that fluoxetine will enable an obese patient to lose weight, with the resulting benefit to the patient's circulation and heart condition, as well as general well being and energy.

Urinary incontinence is classified generally as stress or urge incontinence, depending on whether its root cause is the inability of the sphincter muscles to keep control, or the overactivity of the bladder muscles. Duloxetine controls both types of incontinence, or both types at once, and so is important to the many people who suffer from this embarrassing and disabling disorder.

The present combination is useful for treating many other diseases, disorders and conditions as well, as set out below. In many cases, the diseases to be mentioned here are classified in the International Classification of Diseases, 9th Edition (ICD), or in the Diagnostic and Statistical Manual of Mental Disorders, 3rd Version Revised, published by the American Psychiatric Association (DSM). In such cases, the ICD or DSM code numbers are supplied below for the convenience of the reader.

depression, ICD 296.2 & 296.3, DSM 296, 294.80, 293.81, 293.82, 293.83, 310.10, 318.00, 317.00
migraine
pain, particularly neuropathic pain
bulimia, ICD 307.51, DSM 307.51
premenstrual syndrome or late luteal phase syndrome, DSM 307.90
alcoholism, ICD 305.0, DSM 305.00 & 303.90
tobacco abuse, ICD 305.1, DSM 305.10 & 292.00
panic disorder, ICD 300.01, DSM 300.01 & 300.21
anxiety, ICD 300.02, DSM 300.00
post-traumatic syndrome, DSM 309.89
memory loss, DSM 294.00
dementia of aging, ICD 290
social phobia, ICD 300.23, DSM 300.23
attention deficit hyperactivity disorder, ICD 314.0
disruptive behavior disorders, ICD 312
impulse control disorders, ICD 312, DSM 312.39 & 312.34
borderline personality disorder, ICD 301.83, DSM 301.83
chronic fatigue syndrome
premature ejaculation, DSM 302.75
erectile difficulty, DSM 302.72
anorexia nervosa, ICD 307.1, DSM 307.10
disorders of sleep, ICD 307.4
autism
mutism
trichotillomania

As used herein the term "sexual dysfunction" refers to a decrease in sexual functioning or a decrease in sexual interest or desire, or a combination of both a decrease in sexual functioning and a decrease in sexual interest or desire. For example, sexual dysfunction includes the following symptoms alone or in any combination; a decrease in the ability to become sexually excited, an increased latency of time to achieve orgasm, an inability to

achieve orgasm, a decrease in the male's ability to get an erection or to maintain an erection, failure of the male to obtain an erection, decreased libido, and the like.

It is understood that the term "sexual dysfunction" includes within its scope "substance-induced sexual dysfunction". The term "substance-induced sexual dysfunction" as defined by the DSM-IV™, American Psychiatric Association, page 519-521, 1994, incorporated herein by reference, refers to a clinically significant sexual dysfunction that results in marked distress or interpersonal difficulty. The sexual dysfunction is judged to be fully explained by the direct physiological effects of a substance (i.e., a drug of abuse, a medication, or toxin exposure). In addition, the sexual dysfunction is not better accounted for by a sexual dysfunction that is not substance-induced.

Thus, an improvement in sexual dysfunction means there has been an increase in sexual functioning or an increase in sexual interest or desire, or a combination of both an increase in sexual functioning and an increase in sexual interest or desire. For example, an improvement in sexual dysfunction includes the following symptoms alone or in any combination; an increase in the ability to become sexually excited, a decreased latency of time to achieve orgasm, an increased ability to achieve orgasm, an increase in the male's ability to get an erection or to maintain an erection, increased libido, and the like.

As used herein the term "gastrointestinal side effect" includes but is not limited to nausea, vomiting or diarrhea, or any combination thereof.

Administration

The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of

the patient, including diseases other than that for which the physician is treating the patient. As used herein the term "effective amount" is the amount or dose of the compound which provides the desired effect in the patient under diagnosis or particular treatment, such as treatment for depression. General outlines of the dosages, and some preferred dosages, can and will be provided here. Dosage guidelines for some of the drugs will first be given separately; in order to create a guideline for any desired combination, one would choose the guidelines for each of the component drugs.

Zatosetron: about 0.25 to 200 mg, once/day; preferred, about 0.5 to 100 mg, once/day; most preferably about 0.5 to 50 mg once/day; and most especially preferred about 0.5 to 10 mg once/day.

Olanzapine: about 0.25 to 200 mg, once/day; preferred, about 1 to 40 mg, once/day; most preferably about 2.5 to 30 mg once/day; and most especially preferred about 5 to 25 mg once/day.

Fluoxetine: from about 1 to about 80 mg, once/day; preferred, from about 10 to about 40 mg once/day; preferred for bulimia and obsessive-compulsive disease, from about 20 to about 80 mg once/day;

Duloxetine: from about 1 to about 30 mg once/day; preferred, from about 5 to about 20 mg once/day;

Venlafaxine: from about 10 to about 150 mg once-thrice/day; preferred, from about 25 to about 125 mg thrice/day;

Milnacipran: from about 10 to about 100 mg once-twice/day; preferred, from about 25 to about 50 mg twice/day;

Citalopram: from about 5 to about 50 mg once/day; preferred, from about 10 to about 30 mg once/day;

Fluvoxamine: from about 20 to about 500 mg once/day; preferred, from about 50 to about 300 mg once/day;

Paroxetine: from about 20 to about 50 mg once/day; preferred, from about 20 to about 30 mg once/day.

Sertraline: from about 20 to about 500 mg once/day; preferred, from about 50 to about 200 mg once/day;

In more general terms, one would create a combination of the present invention by choosing a dosage of first and second components according to the spirit of the above guideline.

As used herein the term "patient" refers to a warm-blooded mammal such as a dog, rat, mouse, human and the like. The preferred patient is a human.

The adjunctive therapy of the present invention is carried out by administering a first component together with the second component in any manner which provides effective levels of the compounds in the body at the same time. All of the compounds concerned are orally available and are normally administered orally, and so oral administration of the adjunctive combination is preferred. They may be administered together, in a single dosage form, or may be administered separately.

However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. One of the drugs may be administered by one route, such as oral, and the others may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

The adjunctive combination may be administered as a single pharmaceutical composition, and so pharmaceutical compositions incorporating both compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally usable pharmaceutical compositions are particularly preferred. Such adjunctive pharmaceutical compositions contain an effective amount of each of the

compounds, which effective amount is related to the daily dose of the compounds to be administered. Each adjunctive dosage unit may contain the daily doses of all compounds, or may contain a fraction of the daily doses, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compounds. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compounds. The amounts of each drug to be contained in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the adjunctive therapy is being given.

The inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional, except for the presence of the combination of the present invention. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the adjunctive combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations may be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert

powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments.

Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as enteric compositions, and even more preferred to formulate them as enteric pellets.

A preferred duloxetine enteric formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional separating layer; c) an enteric layer comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a pharmaceutically acceptable excipient; d) an optional finishing layer. This enteric formulation is described in U.S. Patent No. 5,508,276, herein incorporated by reference in its entirety.

Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are

also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

The following typical formulae are provided for the interest and information of the pharmaceutical scientist.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Zatosetron	25 mg
Fluoxetine, racemic, hydrochloride	20
Starch, dried	150
Magnesium stearate	10
Total	210 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Zatosetron	10
Fluoxetine, racemic, hydrochloride	10
Cellulose, microcrystalline	275
Silicon dioxide, fumed	10
Stearic acid	5
Total	310 mg

Formulation 3

Capsules are made as follows:

Zatosetron	70 mg
Fluoxetine, racemic, hydrochloride	30 mg
Starch	39 mg
Microcrystalline cellulose	39 mg
Magnesium stearate	2 mg
Total	180 mg

Formulation 4

Suppositories are made as follows:

Zatosetron	75 mg
(+)-Duloxetine, hydrochloride	5 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,080 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 5

Suspensions are made as follows:

Zatosetron	20 mg
Sertraline	100 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 6

An intravenous formulation may be prepared as follows:

Zatosetron	20 mg
Paroxetine	25 mg
Isotonic saline	1,000 ml

We claim:

1. A method for treating a patient suffering from depression, comprising administering to said patient an effective amount of a first component which is a 5-HT_3 receptor antagonist, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor.

2. A method of Claim 1 wherein the first component is chosen from the group consisting of Zatosetron, Olanzapine, Ondansetron, Granisetron, Bemesetron, Tropisetron, FK1052, YM-060, and MDL 72222; and the second component is selected from the group consisting of fluoxetine, venlafaxine, citalopram, fluvoxamine, paroxetine, sertraline, milnacipran and duloxetine.

3. A method of Claim 1 wherein the first component is Zatosetron.

4. A method of Claim 1 wherein the second component is fluoxetine.

5. A method for treating a patient suffering from depression, comprising administering to said patient an effective amount of a first component which is Zatosetron, in combination with an effective amount of a second component which is fluoxetine.

6. A method according to claim 5 wherein sexual dysfunction associated with the second component is improved.

7. A method according to claim 5 wherein gastrointestinal side effects associated with the second component are reduced.

8. A method according to claim 7 wherein the gastrointestinal side effects are nausea or vomiting.

9. A pharmaceutical composition which comprises a first component which is a 5-HT_3 receptor antagonist, and a second component which is a serotonin reuptake inhibitor.

10. A composition of Claim 9 which comprises a first component which is Zatosetron, in combination with a second component chosen from the group consisting of fluoxetine, venlafaxine, citalopram, fluvoxamine, paroxetine, sertraline, milnacipran and duloxetine.

11. A composition of Claim 9 which is adapted for oral administration.

12. A composition of Claim 9 wherein the first component is Zatosetron.

13. A composition of Claim 12 wherein the second component is fluoxetine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/10092

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/55, 31/44, 31/415, 31/445, 31/34, 31/15, 31/135
US CL :514/220, 304, 397, 321, 323, 469, 640, 649, 657
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/220, 304, 397, 321, 323, 469, 640, 649, 657

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,973,594 A (TYERS) 27 November 1990, see the abstract.	1-13
Y	The Merck Index - 11th Edition. Edited by BUDAVARI, SUSAN, Rahway, New Jersey: Merck & Co., Inc., 1989, page 655.	1-13
Y	Database DRUGU on STN, Derwent Information Ltd., No. 91-33754, FULLER, R.W. 'Role of Serotonin in Therapy of Depression and Related Disorders,' abstract, J. Clin. Psychiatry, 52(5) Suppl., 52-57, 1991.	1-13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
02 AUGUST 1999

Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/10092

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database BIOSIS on STN, Biological Abstracts Service, No. 1994-504123, MIYATA, K. et al. 'Serotonin (5-HT)-3 receptors: Antagonists and their pharmacological profiles,' abstract, Folia Pharmacologica Japonica, 1994, 104(3), 143-152.	1-13
Y	Database DRUGU on STN, Derwent Information Ltd., No. 97-45747, MILLER, D. D. et al. 'Effect of Antipsychotics on regional cerebral blood flow measured with positron emission tomography,' abstract, Neuropsychopharmacology, 1997, 17(4), 230-240.	1-13
Y	Database Medline on STN, US National Library of Medicine (Bethesda, MD, USA), No. 98170902, WEISLER, R. H. et al. 'Adjunctive use of olanzapine in mood disorders: five case reports,' abstract, Annals of Clinical Psychiatry, December 1997 9(4) 259-262.	1-13
Y	Database DRUGU on STN, Derwent Information Ltd., No. 97-44995, DEVANE, C. L. et al, 'Fluvoxamine-induced theophylline toxicity,' abstract, American Journal of Psychiatry, 1997, 154(9), 1317-1318.	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/10092

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN (REG, CA, BIOSIS, MEDLINE, DRUGU, EMBASE)
search terms: depression, 5-HT3 receptor antagonist (zatosetron, olanzapine, ondansetron, etc.), serotonin reuptake inhibitor (fluoxetine, venlafaxine, etc.)